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***Case Control Study***

**Efficacy and safety of short duration radiotherapy combined with chemotherapy for advanced rectal cancer**

Gao SQ *et al*. Radiotherapy and chemotherapy for advanced rectal cancer

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**Abstract**

BACKGROUND

Radiotherapy or chemoradiotherapy is widely used for the treatment of rectal cancer preoperatively. Although the combination of radiotherapy and chemotherapy as an established preoperative neoadjuvant therapy shows high efficacy in the treatment of rectal cancer, some patients experience a response of poor tolerance and outcomes due to the long duration radiotherapy. The study compared short duration radiotherapy plus chemotherapy *vs* long duration radiotherapy plus chemotherapy for rectal cancer to determine whether short duration radiation treatment should be considered to diminish complications, reduce risk of recurrence and improve survival in patients with rectal cancer.

AIM

To evaluate the efficacy and safety of short duration radiotherapy combined with chemotherapy for the treatment of advanced rectal cancer.

METHODS

One hundred patients with stage IIIB or higher severe rectal cancer were selected as the study subjects at The First Affiliated Hospital of Hebei North University between December 2018 and December 2019. The patients were assigned to different groups based on the treatment regimens. Fifty patients who received preoperative short durations of radiotherapy plus chemotherapy were enrolled in an observation group and fifty patients who received conventional radiotherapy and chemotherapy were enrolled in a control group. Colonoscopic biopsy was performed for all patients with pathological diagnosis of rectal cancer. The expression of tumor-related factors such as RUNX3 and Ki-67 was quantitatively analyzed using immunohistochemistry in the tissues of the patients before and after treatment. Moreover, the duration of procedure, the amount of bleeding during the operation, the anus-conserving rate, the incidence of postoperative complications (wound infection, anastomotic leakage, postoperative intestinal obstruction, *etc*.) and postoperative pathology were compared between the two groups. The overall survival rate, recurrence rate and distant metastasis rate were also compared through postoperative reexamination and regular follow-up.

RESULTS

There was no significant difference in the positive expression rate of RUNX3 and Ki-67 between the two groups before the treatment (*P* > 0.05). Compared with the pretreatment value, the positive rate of RUNX3 was increased and the positive rate of Ki-67 was decreased in both groups after the treatment (all *P* < 0.05). The incidence of leukopenia, thrombocytopenia, neutropenia and diarrhea were higher in the observation group than in the control group (all *P* < 0.05). There was no significant difference in the incidence of anemia, fatigue, neurotoxicity and nausea and vomiting between the two groups (all *P* > 0.05). No significant difference was observed in the duration of procedure, intraoperative bleeding, the anus-conserving rate and the incidence of postoperative complications between the two groups (*P* > 0.05). After 1 year of follow-up, the 1-yr survival rate was 80.0% in the observation group and 68.0% in the control group, the recurrence rate was 8.0% in the observation group and 10.0% in the control group, the distant metastasis rate was 6.0% in the observation group and 8.0% in the control group difference (all *P* < 0.05).

CONCLUSION

Short duration radiotherapy combined with chemotherapy can improve the cure rate, prolong the survival time and reduce the incidence of complications in patients with advanced rectal cancer.

**Key Words:** Short course radiotherapy; Chemotherapy; Advanced rectal cancer; Runx3; Ki-67

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**Core Tip:** Short duration radiotherapy was compared to conventional fractionated radiation treatment plus chemotherapy in 100 patients with stage IIIB or more severe rectal cancer to verify whether short duration preoperative radiotherapy had an advantage in diminishing complications, reducing risk of recurrence and improving survival. The findings revealed that there was no significant difference in the incidence of complications between short and long duration radiotherapy plus chemotherapy. However, short duration radiotherapy improved the 1-yr survival rate and reduced the recurrence rate and distant metastasis rate in comparison with conventional preoperative radiotherapy.

**INTRODUCTION**

The morbidity and mortality of rectal cancer tend to increase year by year in China. Effective initial screening methods for this disease have been limited. Most patients with rectal cancer visit the hospital with progressive disease and are staged as moderate or advanced, which leads to high cost, poor effectiveness and poor long-term survival. Meanwhile, it has placed a heavy strain on patients themselves, their family members and society[1-3]. Although the combination of radiotherapy and chemotherapy as an established preoperative neoadjuvant therapy shows high efficacy in the treatment of rectal cancer, some patients experience a response of poor tolerance and safety due to the long duration preoperative neoadjuvant therapy[4,5]. Seeking out the optimal therapeutic regimen is helpful to reduce the duration of preoperative adjuvant treatment and lower the incidence of complications during the treatment. Then the recovery rate is improved and survival time is prolonged accordingly by discussing the effectiveness of short durations of radiotherapy combined with chemotherapy in patients with rectal cancer.

**MATERIALS AND METHODS**

***General information of study participants***

One hundred patients with stage IIIB or more severe rectal cancer were selected as the study subjects between December 2018 and December 2019. They were divided into two groups based on different treatment regimens received. Among them, 50 patients who received preoperative short durations of radiotherapy plus chemotherapy were included in an observation group and 50 patients who received conventional radiotherapy and chemotherapy were included in a control group.

The patients included in the study were between 30 and 70 years of age without definite distant metastasis, other cancer comorbidities, surgical contraindications, cardiovascular diseases and other severe diseases. For all the participants, the participation in the study was voluntary. The rectal tumor was located close to the anus (< 12 cm from the anal verge). They were diagnosed with stage IIIB rectal cancer by colonoscopic biopsy pathology results.

Of 50 patients in the observation group, 31 were men and 19 were women. The age range of patients was between 46 and 66 (53.12 ± 9.45) years of age. In terms of tumor staging, 30 were stage IIIB, and 20 were stage Ⅳ. Karnofsky performance status score was < 40 in 7 patients, 40 to 60 in 24 patients and > 60 in 16 patients.

Of 50 patients in the control group, 28 were men and 22 were women. The age range of patients was between 48 and 67 years of age. In terms of tumor staging, 32 were stage IIIB, and 18 were stage Ⅳ. Karnofsky performance status score was < 40 in 8 patients, 40 to 60 in 24 patients and > 60 in 18 patients. There was no significant difference in general information of the patients including gender, age, cancer staging and Karnofsky performance status score between the two groups (*P* > 0.05). The study was approved by the ethics committee of our hospital and written informed consent was obtained from each patient.

***Treatment methods***

The observation group received short duration radiotherapy and chemotherapy and the control group received conventional chemoradiotherapy before the operation[6,7]. For the short duration radiotherapy, a total dose of 25 Gy was delivered with 5 Gy daily for 5 d, and the operation was performed within 5 d after the radiotherapy. For the conventional radiation therapy, approximately 45 to 50 Gy was given with 1.8 to 2.0 Gy daily, 5 d per week, for 25 to 28 treatments, and the operation was performed within 4 to 8 wk after the treatment. Total mesorectal excision was performed in both groups by the same medical team.

***Measures***

The expression of Runx3 and Ki-67 was compared between the two groups of patients undergoing biopsy test. Immunohistochemical assay was used to quantitatively analyze the expression of biomarkers Runx3 and Ki-67. The positive expression of Runx3 was defined as yellowish-brown staining of the nucleus and cytoplasm. The extent of staining grading scale was as follows: 0 = positive cell was not discovered or only yellowish-brown cytoplasm was discovered, and the number of cells of nucleus stained was ≤ 1 per high power field; 1 = mild staining; 2 = moderate staining; and 3 = severe staining. The scale assigning a score for the percentage of cells with positive expression was as following: 0 = no staining; 1 = the number of stained cells was ≤ 25%; 2 = the number of stained cells was between 26% and 50%; 3 = the number of stained cells was > 50%. If the score for extent and severity of staining and the percentage of cells with positive expression gave a product of ≥ 2, the expression of Runx3 was considered as positive. Ki-67 expression was determined by the following criteria. Five different fields of view under high power field were randomly selected. The total number of cells as well as the number of cells stained was observed within field of view to derive the staining rate. The equation for staining rate was as following: staining rate (%) = (the number of cells stained/the total number of cells) × 100%. Positive expression of Ki-67 was identified by staining rate > 10%.

The incidence of chemoradiotherapy-associated adverse reactions before the operation was compared between the two groups. Common adverse reactions including anemia, fatigue, neurotoxicity, nausea and vomiting, leukopenia, thrombocytopenia, neutropenia and diarrhea were observed.

The operation/procedure indices were compared between the two groups including the duration of operation, intraoperative blood loss, anal conservation rate and postoperative complications (surgery incision infection, anastomotic leakage, intestinal obstruction, *etc*.). The participants were followed-up for 1 year and 1-yr survival, recurrence and distant metastasis were calculated and compared between the two groups.

In terms of statistical methods, SPSS 22.0 was used to process the data. Measurement data that was subject to normal distribution was expressed using mean ± standard deviation, and intergroup differences were compared using Student’s *t* test. For those data that were not subject to normal distribution, nonparametric Mann-Whitney rank-sum test was used. Enumeration data was expressed by using %, and intergroup difference was compared using *χ*2 tests. *P* < 0.05 represented a significant difference.

**RESULTS**

***Expression of Runx3 and Ki-67***

There was no significant difference in the expression of Runx3 and Ki-67 at biopsy between the two groups before the treatment (*P* > 0.05). Compared with those before the treatment, the positive rate of Runx3 expression was increased and the positive rate of Ki-67 expression was decreased in both groups after the treatment (all *P* < 0.05, Table 1).

***Chemoradiotherapy-induced adverse reactions***

By comparing the incidence of adverse reactions between the two groups before the operation, it revealed that the incidence of leukopenia, thrombocytopenia, neutropenia and diarrhea was higher in the observation group than in the control group (*P* < 0.05, Table 2). However, there was no significant difference in the incidence of anemia, fatigue, neurotoxicity and nausea and vomiting between the two groups (*P* > 0.05).

***Operation indices***

No significant difference was observed in the duration of surgery, intraoperative blood loss, rate of anus conservation and postoperative complications between the two groups after comparison of the operation indices (*P* > 0.05, Table 3).

***One-year survival, recurrence and distant metastasis***

After a follow-up of 1 year, 1-yr survival was 80.0% (40/50) in the observation group and 68.0% (34/50) in the control group. The recurrence rate was 8.0% (4/50) in the observation group and 10.0% (5/50) in the control group. The distant metastasis rate was 6.0% (3/50) in the observation group and 8.0% (4/50) in the control group (*P* > 0.05).

**DISCUSSION**

The requirements for health are increasing with the improvement of quality of life. However, a large fraction of people lead an unhealthy lifestyle, which leads to high-risk rectal cancer. Chemoradiotherapy combined with surgery remains the main therapy for this disease. Although many studies have explored the efficacy of short duration radiotherapy combined with chemotherapy for the treatment of advanced rectal cancer, the focus varies among these studies[8-10]. Some studies examined local resection rate in early low rectal cancer and others analyzed the short-term efficacy and adverse reactions of these treatments. The present study discussed the efficacy of short duration radiotherapy combined with chemotherapy for advanced rectal cancer in order to find more suitable treatments[11-13].

The occurrence and development of colorectal cancer is regulated and controlled by multiple genes. Among them, Runx3 and Ki-67 play an important role in the occurrence, development, metastasis and prognosis of colorectal cancer[14]. Downregulation of deactivation of Runx3 gene transcription may lead to evolution and progression of several tumors. Runx3 is localized on chromosome 1p36.1 and is atumor suppressor gene. It can directly compound activation through signal transduction of transforming growth factor to switch from membrane to specific targeted sites of nucleus. Under the direction of Runx3 protein, compounds will bind to targeted sites and activate genes to achieve cell differentiation, cycle regulation, pro-apoptosis and malignant transformation. Inactivation may cause the signal transduction pathway to be out of control, which further induces inhibition of apoptosis and even the evolution and progression of tumors.

Ki-67, a nuclear protein, is associated with RNA transcription and proliferation within cells. The expression of Ki-67 is high in the period of cell differentiation and proliferation, which reflects the extent of cell differentiation and proliferation. The expression of Ki-67 is associated with the development of various tumors. Moreover, the expression levels of Ki-67 are significantly associated with the prognosis of colorectal liver metastases. The current study revealed that the expression of Runx3 was increased and the expression of Ki-67 was decreased in both groups after the treatment compared with those before the treatment, suggesting short duration radiotherapy and chemotherapy can effectively inhibit the progression of tumors and improve the treatment outcomes.

Short duration radiotherapy could effectively kill the proliferating cells outer layer of tumor in spite of high dose of single radiation and in such a short time. In addition, short duration radiation can effectively avoid the effect of radiation-induced complications on subsequent surgery, and duration of therapy and treatment-free intervalsis shortened due to the simple and easy operation, which can reduce economic burden and improve postoperative therapeutic efficacy[15-17]. This study indicated that short duration radiotherapy combined with chemotherapy can effectively reduce the incidence of leukopenia, thrombocytopenia, neutropenia and diarrhea in patients with advanced rectal cancer. Short duration radiotherapy combined with chemotherapy can beneficially relieve postoperative complications and improve quality of life in patients with advanced rectal cancer[18-21]. Furthermore, operation indices were similar between short duration radiotherapy combined with chemotherapy and convention chemoradiotherapy, suggesting that short duration radiotherapy combined with chemotherapy is safe and is worthy of promotion[18,19]. In addition, there is little difference in 1-yr survival, recurrence and distant metastasis rates between the two groups, which could be accounted by the short study duration.

**CONCLUSION**

In the future study, length of time for the periods of study observation should be prolonged to further discuss the long-term rehabilitation outcomes of short duration radiotherapy combined with chemotherapy.

**ARTICLE HIGHLIGHTS**

***Research background***

Short duration radiation treatment may have a valuable role in the treatment of patients assessed as too frail to undergo long duration chemoradiation. Studies have compared short duration *vs* long duration radiation treatment for rectal cancer. However, the results are contradictory. The present study explored the efficacy and safety of short duration radiation treatment for advanced rectal cancer.

***Research motivation***

The present study sought the optimal duration of radiation therapy for advanced rectal cancer to improve survival time and reduce complications and recurrence by comparing short duration *vs* long duration radiotherapy in patients with advanced rectal cancer.

***Research objectives***

This study aimed to discuss the efficacy and safety of short duration radiotherapy combined with chemotherapy for the treatment of advanced rectal cancer.

***Research methods***

This study compared short duration radiation treatment (5 Gy in 5 fractions) with conventional long duration chemoradiation (1.8 to 2.0 Gy in 25 to 28 fractions) in 100 patients with IIIB or IV rectal cancer between December 2018 and December 2019. Expression of Runx3 and Ki-67, chemoradiotherapy-induced adverse reactions, operation indices, 1-yr survival, recurrence and distant metastasis were researched to see whether there was an advantage in the short duration radiation treatment group.

***Research results***

Almost no statistically significant differences were observed in the incidence and operation indices when comparing short duration radiation treatment with conventional long duration chemoradiation. However, the 1-yr survival rate was higher and the recurrence rate and distant metastasis rate were lower in the short duration radiation group than in the long duration group.

***Research conclusions***

Based on the results, short duration radiation treatment seems to be effective for the treatment of advanced rectal cancer. In addition, clear survival benefits were observed with low incidence of recurrence and distant metastasis in the short duration radiation group.

***Research perspectives***

Further studies in a multidisciplinary setting are warranted to identify whether the more convenient short duration radiation treatment should be considered if there are clear concerns regarding a patient’s physical or psychosocial ability to tolerate long duration chemoradiation to determine the most appropriate individualized therapeutic strategy.

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**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of the First Affiliated Hospital of Hebei North University.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** No conflict of interest for all authors.

**Data sharing statement:** No additional to be shared.

**STROBE statement:** The authors have read the STROBE Statement checklist of items, and the manuscript was revised according to the STROBE Statement-checklist of items.

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**Table 1 Differences in the expression of Runx3 and Ki-67 from the biopsy between two groups before and after the treatment, *n* (%)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Groups** | ***n*** | **Time point** | **Runx3** | | **Ki-67** | |
| **Positive** | **Negative** | **Positive** | **Negative** |
| Observation group | 50 | Before the treatment | 26 (2.0) | 24 (48.0) | 46 (92.0) | 4 (8.0) |
|  |  | After the treatment | 38 (76.0)a | 12 (24.0) | 37 (74.0)a | 12 (26.0) |
| Control group | 50 | Before the treatment | 27 (54.0) | 23 (46.0) | 45 (90.0) | 5 (10.0) |
|  |  | After the treatment | 34 (68.0)a | 16 (32.0) | 36 (72.0)a | 14 (28.0) |

Compared with those before the treatment, a*P* < 0.05.

**Table 2 Differences in the incidence of chemoradiotherapy-induced adverse reactions between the two groups before the operation, *n* (%)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Groups** | ***n*** | **Anemia** | **Leukopenia** | **Thrombocytopenia** | **Neutropenia** | **Diarrhea** | **Fatigue** | **Neurotoxicity** | **Nausea and vomiting** |
| Observation group | 50 | 24 (48.0) | 31 (62.0)a | 36 (72.0)a | 31 (62.0)a | 17 (34.0)a | 9 (18.0) | 11 (22.0) | 23 (46.0) |
| Control group | 50 | 22 (44.0) | 20 (40.0) | 24 (48.0) | 22 (44.0) | 9 (18.0) | 8 (16.0) | 12 (24.0) | 22 (24.0) |

Compared with the control group, a*P* < 0.05.

**Table 3 Comparison of operation indices between the two groups, *n* (%)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Groups** | ***n*** | **Duration of surgery (min)** | **Intraoperative blood loss (mL)** | **Anal conservation rate** | **Postoperative complications** | | |
| **Surgery incision infection** | **Anastomotic leakage** | **Intestinal obstruction** |
| Observation group | 50 | 234.12 ± 24.56 | 124.78 ± 15.90 | 45 (90.0) | 2 (4.0) | 3 (6.0) | 2 (4.0) |
| Control group | 50 | 215.34 ± 26.71 | 113.61 ± 16.22 | 44 (88.0) | 3 (6.0) | 4 (8.0) | 1 (2.0) |
| *t*/*χ2* value |  | 1.21 | 1.98 | 0.28 | 0.11 | 0.19 | 0.21 |
| *P* value |  | 0.54 | 0.21 | 0.75 | 0.87 | 0.83 | 0.74 |